TOXICOLOGICAL PROPERTIES OF SEVERAL COMMERCIALLY AVAILABLE SURFACTANTS

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Surfactants are used in formulations varying in purpose from industrial floor cleaners, to compositions for cleaning the most delicate natural or synthetic fibers, to cosmetics. When one is considering a surfactant for a new formulation or for any purpose, he has a myriad of commercially available products from which to choose.

It is of primary importance, of course, that he select a product that will do a good job from a functional point of view. Since there may be a number of acceptable products in this regard he may wish to consider the one which will offer him the greatest margin of safety from the standpoint of the health of his customers and employees. The matter of health and safety will be influenced to a great extent by the application for which his formulation is intended. If his product is a cosmetic, for example, it is likely that his prime concern will be that of safety.

The tests herein reported were designed to provide pertinent information about the effects on the skin and eyes and about the toxicity by acute ingestion of several commercially available surfactants. Aqueous dilutions of 1 per cent, 5 per cent and 25 per cent were chosen for study to represent the range of concentration employed in most formulations.

Source and Feeding of Animals

The albino rats used for the acute oral feeding studies were females ranging in weight from 135 to 180 g. and were raised in this laboratory of stock originally obtained from the Wistar Institute of Anatomy and Biology in 1938. They were maintained on Famo Laboratory Ration.

The animals used for eye and skin studies were albino rabbits of heterogeneous stock raised in this laboratory and fed Famo Rabbit Starter and Breeder Pellets.

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Laboratory Methods

Acute Oral Toxicity

Toxicity when ingested in single doses was evaluated by feeding the material as 10 per cent aqueous solutions or emulsions to unfasted rats by intubation. Groups of five animals each were fed doses ranging in geometric progression from 0.252 to 7.95 g./kg. body weight. Mortality was established over a two week post-feeding period. $L.D._{50}$ values were calculated by the Weil Modification of the Method of Thompson.*

Eye Studies

The eyes of all rabbits used in this study were established as being free of corneal injury by selecting those showing no reaction to a 5 per cent aqueous solution of fluorescein disodium salt twenty-four hours prior to use. Two drops of surfactant to be tested were applied to each eye of the rabbit. Within 30 seconds one eye was washed for two minutes with flowing tap water. The other eye was left unwashed. Both eyes were evaluated for immediate effects and again after one hour, twenty-four hours, forty-eight hours and one week for conjunctival and corneal injury and for internal effects such as iritis and lenticular damage. Fluorescein was employed in all cases as an aid in assessing corneal injury. Three animals were used for each concentration studied (25 per cent, 5 per cent and 1 per cent aqueous emulsions or solutions).

The type and intensity of reaction were rated according to the following index code:

Index	Reaction (Objective Observations)	Pain Evaluation (Reactions by Animal)
1	No effect.	No response.
2	Very slight effect, disappearing within twenty-four hours. May consist of appreciable pain initially and some conjunctival irritation. No corneal injury.	No more than a few blinks. Normal in a minute or so.
3	Slight effect, disappearing within a week. May consist of appreciable conjunctival irritation and pain but no corneal or internal injury.	Blinks and tries to open eye. Reflexes close eye.
4	Moderate effect, consisting of superficial corneal injury which clears within a week. Probably no internal effects on eye. No loss of vision expected. Conjunctival irritation may be severe.	Holds eye shut and puts pressure on lids. May rub eye with paw.
5	Severe effect, consisting of serious corneal injury from which recovery will be prolonged. Some impairment of vision may be expected. Internal injury may be observed. Conjunctival irritation may or may not be severe.	Holds eye shut vigorously. May squeal.
6	Very severe effect, consisting of total loss of vision due to serious injury to the cornea or internal structure of the eye. Conjunctival irritation may or may not be severe.	Holds eye shut vigorously. May squeal, claw at eye, jump and try to escape.

* Weil, C. S., *Biometrics*, **8**, 343 (1952).

Skin Studies

Rabbits were prepared by shaving the bellies free of hair with a straight razor and barber soap. After five days, animals free of hair growth were selected as test subjects. Immediately prior to application, abrasions were made with a sharp instrument on the caudal area of the belly. Abrasions were sufficiently deep to penetrate the stratum corneum but not deep enough to result in appreciable bleeding. The test materials were applied to one inch by one inch cotton pads which in turn were held in intimate contact with the intact and abraded skin areas by means of a cloth bandage taped around the entire trunk of the animal. Ten applications of 5 ml. each were made over a period of fourteen days to intact areas. Three similar applications were made to abraded areas. This procedure resulted in continuous contact for fourteen days to intact skin and three days to abraded skin. A small amount of material was likewise applied daily to the intact ear following the application and evaluation program as described for the intact belly. In no case were applications continued beyond the production of a substantial burn or eschar formation. Skin reactions were observed and recorded following each application and at subsequent intervals up to three weeks from the beginning of the study.

The type and intensity of reactions were rated according to the following index code:

Index	Reactions
1	Essentially no irritation to intact skin.
2	Very slight hyperemia on intact skin, likely more irritating to abraded skin.
3	Slight hyperemia on intact skin, may or may not burn abraded skin.
4	Moderate hyperemia on intact skin, may or may not burn abraded skin.
5	Burn from two to four twenty-four hour applications to intact skin.
6	Burn from one twenty-four-hour application to intact skin.

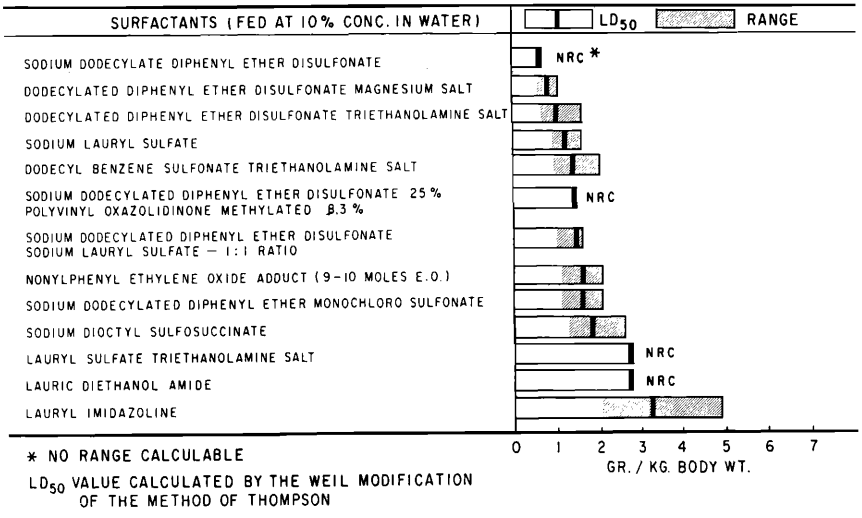
Results and Conclusions

Acute Oral Toxicity

All materials tested are moderate to low in acute oral toxicity. In Table 1 the $L.D._{50}$ values in rats can be seen to range from 0.71 g./kg. body weight in the case of sodium dodecylated diphenyl ether disulfonate to 3.30 g./kg. for lauryl imidazoline. The toxicity by acute ingestion of both sodium dodecylated diphenyl ether disulfonate and sodium lauryl sulfate appears to be appreciably less when in the form of the triethanolamine salt. It is also significant to note that the toxicity of the 1 : 1 mixture of sodium dodecylated diphenyl ether disulfonate and sodium lauryl sulfate is lower than would be expected on the basis of the toxicity of the individual components.

TABLE I

ACUTE ORAL TOXICITY OF SURFACTANTS WHEN FED TO RATS IN SINGLE DOSES

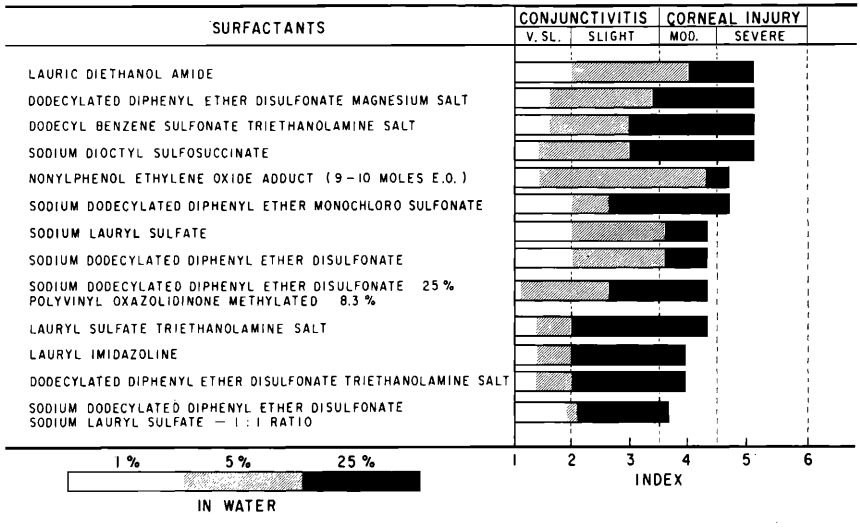


* NO RANGE CALCULABLE

LD_{50} VALUE CALCULATED BY THE WEIL MODIFICATION OF THE METHOD OF THOMPSON

TABLE II

EFFECTS OF SURFACTANTS UPON THE RABBIT EYE



Eye Effects

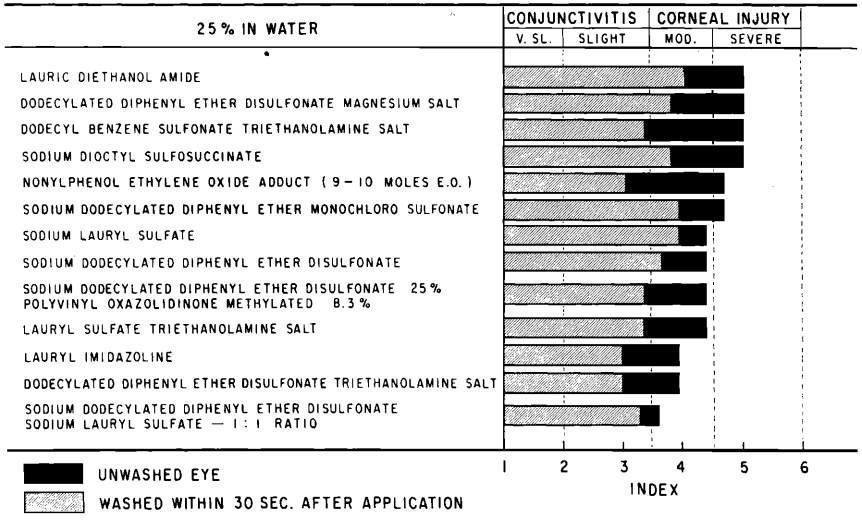
Due to the unique nature of the eye, it is particularly important when considering chemical reactions to ocular tissue to establish the potential for producing loss of sight. Such injury, in its most severe form, involves denaturation of the cornea, resulting in a permanent opaqueness. In extreme cases the iris and lens may be damaged. Less potent chemicals may injure only the conjunctiva, producing some degree of redness, perhaps accompanied by pain and swelling. When considering the intended use of many surfactant formulations, such as hair shampoos, it is reasonable to assume occasional direct eye contact. It is desirable that such products be essentially nonirritating to eye tissues.

The surfactants studied are listed in Table 2 in descending order insofar as their potential for producing ocular injury is concerned. This bar-graph indicates that all materials tested are capable of producing corneal injury at a concentration of 25 per cent in water. In general, those materials with an index above 4.5 possess an appreciable potential for producing severe or permanent impairment of vision as a result of direct eye contact. Those with values between 3.5 and 4.5 would likely produce moderate injury to the cornea. Such injury might be slow to heal, but permanent effects would not be expected.

This bar-graph likewise indicates that all materials are appreciably less injurious to the eye when diluted with water. At 5 per cent concentration only four produced corneal injury of a moderate degree only. At 1 per

TABLE III

EFFECTS OF WASHING RABBIT EYES FOLLOWING APPLICATION OF SURFACTANTS



cent in water none produced more that a transient redness or very slight effect on the conjunctiva. Some were essentially nonirritating to the eye.

It is of particular importance to note the beneficial effects of washing eyes contaminated with surfactants. A comparison between washed and unwashed rabbit eyes is depicted by the bar-graphs in Tables 3 and 4 for concentrations of 25 per cent and 5 per cent, respectively. It can be seen that none of the materials when diluted to 25 per cent would be expected to produce severe injury if a reasonable attempt were made to wash them from the eye and only one when diluted to 5 per cent would be likely to produce any corneal injury whatsoever. Benefits are limited where very slightly or slightly irritating materials are concerned as the washing operation may be as irritating as the materials themselves.

A slight iritis is sometimes observed from eye contact with low concentrations of surfactants but is usually of little consequence. Appreciable injury to the iris and lens frequently accompanies severe corneal injury, in which case the latter is of primary concern due to the potential loss of vision.

Skin Effects

Perhaps of greatest concern, incidental to the handling and use of surfactants, is the potential for producing skin irritation. Many such materials in common use are capable of producing rather severe skin reactions, even chemical burns, under recommended use-conditions of relatively

TABLE IV

EFFECTS OF WASHING RABBIT EYES FOLLOWING APPLICATION OF SURFACTANTS

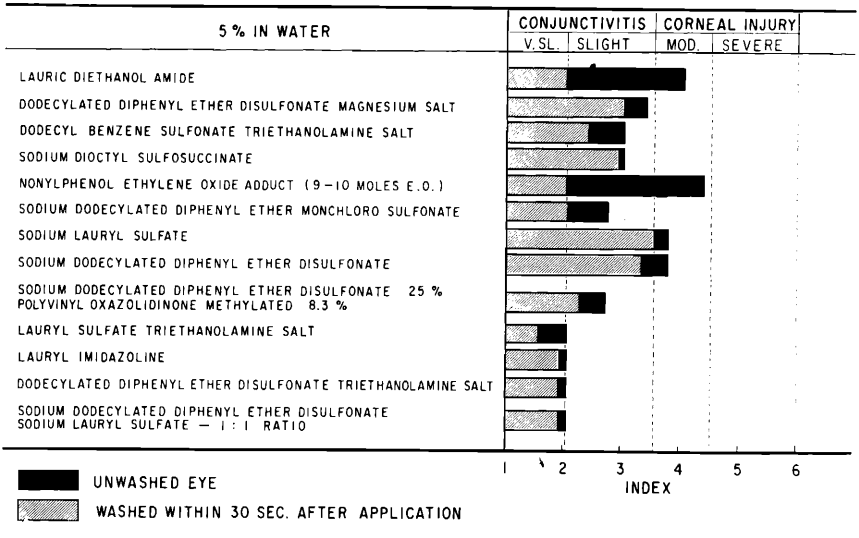


TABLE V

EFFECTS OF SURFACTANTS WHEN APPLIED TO THE RABBIT EAR

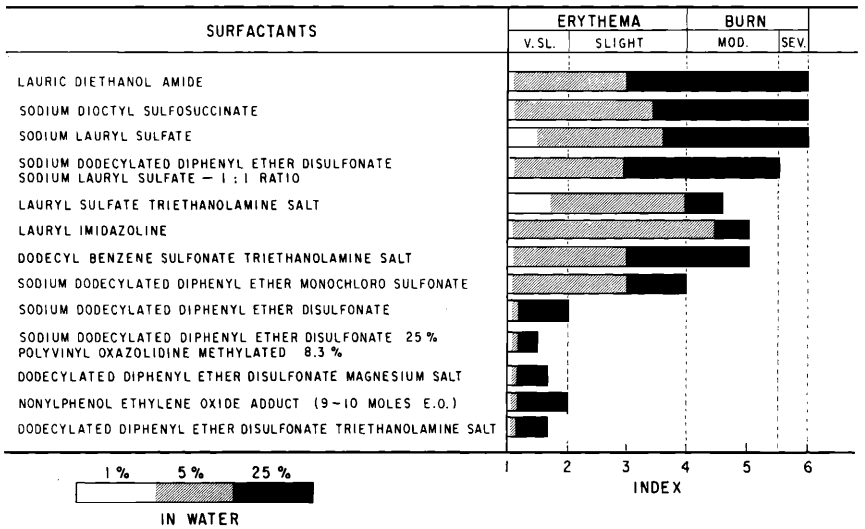
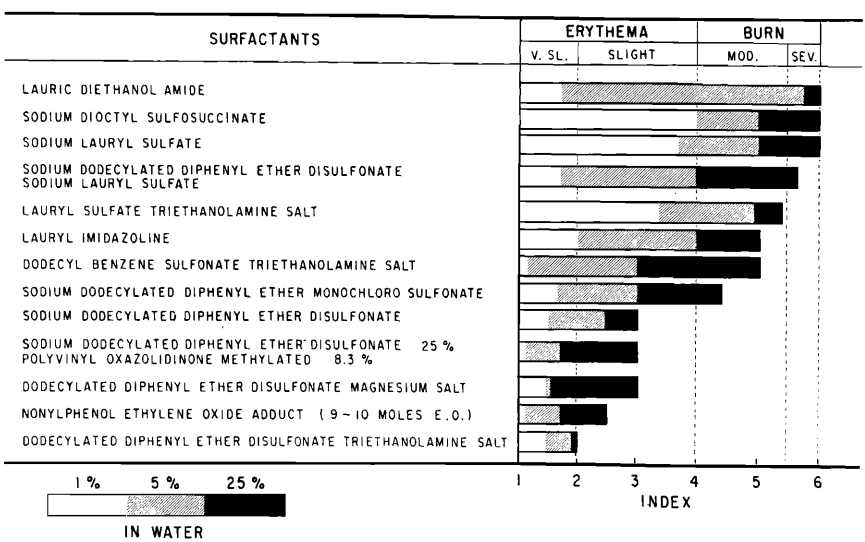


TABLE VI

EFFECTS OF SURFACTANTS WHEN CONFINED TO THE RABBIT BELLY



moderate exposure. The tests conducted in this study were designed to evaluate concentrated and dilute solutions under conditions of both severe and mild exposure.

Table 5 presents the average reaction of three rabbits to repeated, prolonged, applications to the uncovered intact skin of the ear. This technique simulates exposure to uncovered skin which can be assumed to occur with many cosmetic preparations. Table 6 presents results of similar exposure under more rigorous conditions of close confinement to abraded as well as intact skin of the shaved rabbit belly. Such conditions could be encountered from spills or splashes on the clothing or shoes.

The data reveal that four of the materials studied at 25 per cent concentration produced chemical burns upon single, prolonged contact, either when applied to the uncovered skin of the rabbit ear or when confined to the rabbit belly. Several materials possess indexes between 4 and 5.5, which indicates that they may cause burns upon repeated, prolonged contact. Abraded skin is particularly vulnerable to such exposure. The test materials possessing indexes between 2 and 4 have relatively low toxicities insofar as skin irritating properties are concerned. Repeated, prolonged, confined contact with the rabbit belly over a period of fourteen days produced no more than a very slight to slight erythema and even less irritation to the ear. Five of the materials at 25 per cent concentration fall into this class. When reduced to 1 per cent in water all of the test materials proved to be very low in skin irritating potential. Some produced no effect whatsoever upon the ear at 5 per cent concentration and only a very slight effect at 25 per cent.

The data indicate that of the materials tested those least likely to be skin irritants are the ethylene oxide adduct of nonylphenol and the sodium, magnesium and triethanolamine salts of dodecylated diphenyl ether disulfonate, the triethanolamine salt of the latter being the least irritating of all.

Summary

The toxicological properties of several commercially available surfactants have been determined and compared from the viewpoints of acute oral toxicity, eye effects and skin effects.

Since the results show that there are wide differences on all counts between the materials studied, the data presented should be helpful in the selection of surfactants for use in formulations where health and safety are of prime concern.